

Human T-Lymphotropic Virus Type I Associated Myelopathy Treated Effectively with Lymphocytapheresis Using a Leukocyte Removal Filter

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The patient, a 61-year-old woman, received a blood transfusion at the age of 33 years. Weakness of the lower extremities developed at the age of 42 and the diagnosis of human T-lymphotropic virus type I (HTLV-I) associated myelopathy was made. Somatosensory evoked potential examination showed that the latency of P27 evoked by peroneal nerve stimulation was 44 msec. Lymphocytapheresis was performed 3 times with one-week intervals using a leukocyte removal filter. The muscle weakness began to improve on the second day after the second lymphocytapheresis and the sensory impairment began to improve on the third day after the third lymphocytapheresis. The delayed latency of P27 improved after the lymphocytapheresis. The effectiveness of lymphocytapheresis in this case suggests that lymphocytes are involved in the pathogenesis of HTLV-I associated myelopathy.
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Key words: HAM, leukocytapheresis, somatosensory evoked potential

Introduction

Human T-lymphotropic virus type I (HTLV-I) associated myelopathy (HAM), which is reported in Japan (1), Europe (2, 3) and United States of America (4), are thought to be the same disorder as HTLV-I associated tropical spastic paraparesis (TSP) (1). Pathologically, HAM is characterized by chronic progressive parainfectious myelitis with parenchymal infiltration of lymphocytes (5, 6). Although the pathogenesis of HAM has not been elucidated yet, lymphocytes are considered to be involved in the pathogenesis of HAM (7–13). There are a few reports (14–16) on lymphocytapheresis in HAM but most cases were treated with prednisolone previously or concomitantly. Ijichi et al (15) reported that leukocytapheresis stopped the progression of the symptoms of HAM but the effectiveness was mild compared with prednisolone therapy started 3 months after the first leukocytapheresis. This is the first case report in which filtration lymphocytapheresis was performed without previous or concomitant prednisolone therapy in HAM and it was moderately effective.

Case Report

The patient is a 61-year-old woman who was admitted to our hospital with the chief complaint of gait disturbance. She received blood transfusion at the age of 33. Weakness of the lower extremities developed at the age of 42 and progressed gradually. At the age of 54, she began to use a stick to walk. Her past history includes left facial nerve palsy, right ovarian cyst, left ovarian cyst and acute hepatitis. Her family history was unremarkable.

Physical examination was unremarkable. On neurological examination, consciousness was clear and dementia was not present. Mild impairment of hearing was present in both ears. Extraocular movements and sternocleidomastoid muscles were normal. Muscle strength was moderately decreased in both lower extremities and very mildly decreased in the right upper extremity. Muscle atrophy, incoordination and involuntary movement were absent. Mild spasticity in the lower extremities was present. Deep tendon reflexes were highly exaggerated in the lower extremities and mildly exaggerated in the right upper extremity. Trömner reflex and Babinski sign were present bilaterally. The touch, temperature and vibration senses were

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decreased below the Th 6 level but the position sense was normal. Disturbance in urination was present but fecal incontinence was absent.

Blood tests were as follows: Complete blood counts, liver function tests and creatinine were normal. Table 1 shows blood immunological tests which were abnormal before lymphocytapheresis. Albumin 3.7 g/dl, rheumatoid factor IgG (immunoglobulin G) 1.5, anti-lymphocyte antibody (-), anti-myelin antibody (-), cryoglobulin (-), anti-human immunodeficiency virus type 1 antibody (-), virus separation and identification (-). Antibody titers to Epstein-Barr (EB) virus capsid antigen (IgG) 160×, EB virus capsid antigen (IgA) <10×, EB virus early antigen (IgG) 80×, EB virus early antigen (IgA) <10×, EB virus nuclear antigen 10×. Viral antibody titers were examined twice before lymphocytapheresis but they did not show any significant changes. Lymphocyte blastic transformation test with phytohemagglutinin was normal. T cell/B cell percent and CD4/CD8 percent were normal. Human lymphocyte antigen examination revealed A2, A31(19), B39(16), B51(5), Cw7, DR4, DR9.

Cerebrospinal fluid (CSF) examination was as follows: Opening pressure 90 mmCSF, cells 9/mm³, neutrophils/lymphocytes 1/25, protein 31 mg/dl, glucose 56 mg/dl, IgG 15 mg/dl, IgA 2.0 mg/dl, albumin 27.7 mg/dl, myelin basic protein 0.5 ng/ml, oligoclonal IgG band (-), anti-HTLV-I antibody (particle agglutination) 512×, anti-HTLV-I antibody (fluorescent antibody method) 64×, virus separation and identification (-), soluble interleukin-2 receptor 98 U/ml, neopterin 62 pmol/ml (2, 16). Antibody titers to EB virus capsid antigen (IgG) 2×, EB virus capsid antigen (IgA) <1×, EB virus early antigen (IgG)

<1×, EB virus early antigen (IgA) <1×, EB virus nuclear antigen <1×. The antibody index to HTLV-I virus (fluorescent antibody method), calculated from the following formula, was 2.98 and that to EB virus capsid antigen (IgG) was 1.49.

$$\text{antibody index} = \frac{\text{CSF antibody}}{\text{serum antibody}} \div \frac{\text{CSF albumin}}{\text{serum albumin}}$$

Computed tomography scan of the head and magnetic resonance imaging of the head, cervical spine and thoracic spine were normal. Chest roentgenogram, electrocardiogram, and computed tomography scan of the chest were normal. Myelography and nerve conduction velocity were normal. Somatosensory evoked potentials to median nerve stimulation were normal. Central motor conduction time was normal in the hand recording but was unobtainable in the foot recording. Bone scintigram and bone marrow examination were normal. Purified protein derivative test was negative.

Lymphocytapheresis (17) was performed 3 times with one-week intervals using a leukocyte removal filter (Asahi Medical, Tokyo). The patient's blood was continuously drawn at a rate of 50 mg/min; following the addition of 50 mg/h of nafamostat mesilate, it was filtered with the leukocyte removal filter and then returned to the patient. This procedure lasted for 60 minutes. The lymphocyte count did not decrease in the first lymphocytapheresis but it did decrease from 1,341/mm³ to 450/mm³ in the second lymphocytapheresis and from 1,302/mm³ to 346/mm³ in the third lymphocytapheresis (Table 2). The muscle weakness began to improve on the second day after the second lymphocytapheresis and the sensory impairment began

Table 1. Blood Immunological Tests Before the First Lymphocytapheresis and After the Third Lymphocytapheresis

	Before Lymphocytapheresis	After Lymphocytapheresis	Normal range
IgG	2,320	2,280	738-1,244 mg/dl
IgA	867	891	93-296 mg/dl
IgM	193	203	46-153 mg/dl
RA test	+	+	-
RAHA	80	160	<40×
Antiplatelet antibody	+	-	-
Immune complex (anti-C3d antibody)	17.5	9.0	<13 µg/ml
Immune complex (monoclonal RF)	6.0	4.7	<4.2 µg/ml
Anti-HCV antibody (EIA)	1.4	1.4	<0.9
Anti-HTLV-I antibody (PA)	32,768	32,768	<16×
Anti-HTLV-I antibody (FA)	2,560	2,560	<5×
HTLV-I provirus DNA assay pX	+	+	-
Lymphocyte blastic transformation test with Con-A	10,563	29,372	20,000-48,000 CPM
Soluble interleukin-2 receptor	1,027	1,393	145-519 U/ml
Neopterin	28	18	2-8 pMol/ml

Con-A: concanavalin A, CPM: count per minute, EIA: enzyme immunoassay, FA: fluorescent antibody method, HCV: hepatitis C virus, PA: particle agglutination, RA: rheumatoid arthritis, RAHA: rheumatoid arthritis hemagglutination, RF: rheumatoid factor.

Table 2. Blood Cell Counts Before and After Each Lymphocytapheresis

	First lymphocytapheresis		Second lymphocytapheresis		Third lymphocytapheresis	
	before	after	before	after	before	after
Lymphocyte count (/mm ³)	2,032	1,886	1,341	450	1,302	346
White blood cell count (/mm ³)	4,000	4,600	4,100	1,090	3,700	800
Platelet count (/mm ³)	11.6×10 ⁴	6.1×10 ⁴	23.1×10 ⁴	4.9×10 ⁴	19.6×10 ⁴	8.9×10 ⁴
Red blood cell count (/mm ³)	350×10 ⁴	335×10 ⁴	379×10 ⁴	368×10 ⁴	360×10 ⁴	309×10 ⁴

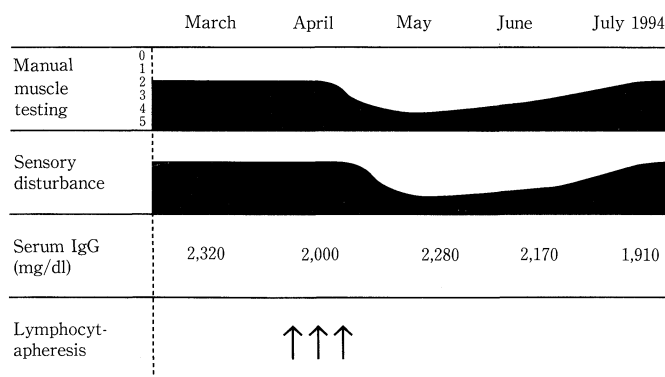


Figure 1. Clinical course. The manual muscle testing began to show improvement on the second day after the second lymphocytapheresis and it improved from 2 to 4 in average. The sensory impairment (touch, temperature and vibration senses) began to improve on the third day after the third lymphocytapheresis and the sensation below the Th 6 level improved from 3/10 to 7/10 in average.

to improve on the third day after the third lymphocytapheresis (Fig. 1). The manual muscle testing showed improvement from 2 to 4 and the disability scale (18) showed improvement from 7 to 4 following lymphocytapheresis. The time to feel the vibration of the tuning fork placed on the lateral malleolus (vibration sense) was improved from 6 seconds to 11 seconds (normal, more than 12 seconds). The effects of lymphocytapheresis lasted for 2–3 months. Somatosensory evoked potential examination showed that the latency of P27 evoked by peroneal nerve stimulation was 44 msec before lymphocytapheresis and that the delayed latency of P27 improved to 39 msec after the lymphocytapheresis (Fig. 2). Lymphocytapheresis did not cause any side effects in this patient.

Discussion

We made the diagnosis of HAM because the patient had chronic spastic paraplegia, a sensory level at Th 6, high titers of anti-HTLV-I antibody in the serum and the CSF and a history of blood transfusion and because the other diseases were denied from the magnetic resonance imaging of the cervical spine and the thoracic spine, etc.

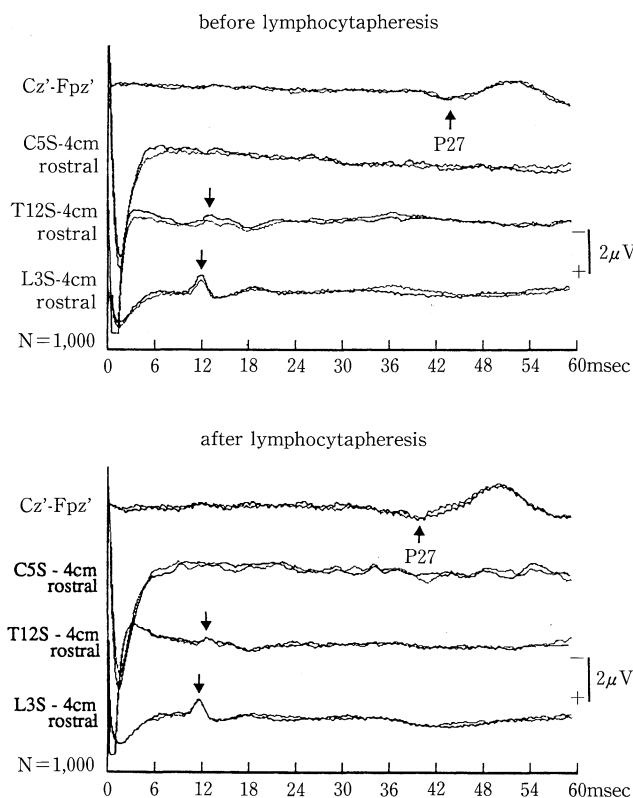


Figure 2. Somatosensory evoked potentials to the peroneal nerve stimulation. Before lymphocytapheresis (March 15, 1994), P27 was delayed to 44 msec. After lymphocytapheresis (May 5, 1994), the latency of P27 was improved to 39 msec.

The antibody index has been used to differentiate whether the antibody was produced within the central nervous system or the antibody was leaked from the serum into the CSF (19). The antibody index to HTLV-I virus (fluorescent antibody method) in the present case was 2.98, suggesting that anti-HTLV-I antibody was produced within the central nervous system (19). This finding is consistent with the report that HTLV-I proviral deoxyribonucleic acid is frequently detected in central nervous system tissue obtained at autopsy from patients with HAM (20).

Antibody titers to EB virus capsid antigen (IgG), EB virus early antigen (IgG) and EB virus capsid antigen (IgA) in the serum are reported to be more frequently increased in HAM

patients than in control subjects (6) and low levels of antibody to EB virus capsid antigen (IgG) in the CSF are reported to be more frequently found in HAM than in control subjects (21, 22). In the present case, antibody titers to EB virus capsid antigen (IgG), EB virus early antigen (IgG) and EB virus nuclear antigen in the serum were increased and a low level of antibody to EB virus capsid antigen (IgG) was found in the CSF. However, the antibody index of EB virus capsid antigen (IgG) was 1.49. This suggests that the antibody was leaked from the serum into the CSF (19) and that EB virus did not play an important role within the central nervous system in our patient.

Prednisolone has been used for the treatment of HAM but recently other therapies such as lymphocytapheresis (14–16), interferon-alpha (23), plasmapheresis (24) and vitamin C (25) have been reported to be effective. The effective rate of lymphocytapheresis in HAM is reported to be almost the same as that of prednisolone and the side effects of lymphocytapheresis are reported to be fewer than with prednisolone treatment (16). In the present case, blood immunological tests such as IgG, IgA, IgM, immune complex (anti-C3d antibody), immune complex (monoclonal RF), lymphocyte blastic transformation test with concanavalin A, soluble interleukin-2 receptor (26), soluble CD4 (27) and neopterin (28, 29) were abnormal (Table 1). Therefore, we performed lymphocytapheresis with the informed consent of the patient.

In the present case, the symptoms (Fig. 1), somatosensory evoked potential test (Fig. 2), immune complex (anti-C3d antibody), lymphocyte blastic transformation test with concanavalin A, soluble CD4 and serum neopterin (Table 1) showed an improvement after lymphocytapheresis. The lymphocytapheresis was the first and the only therapy of HAM in our case and it was effective without any side effects, although the effect of lymphocytapheresis lasted only for 2–3 months. The mechanism of effectiveness of lymphocytapheresis is not clear although it is considered to be related to cellular immunity (16). The improvement of not only the neurological symptoms but also the P27 latency in the present case suggests that the improvement is not a placebo effect but an amelioration of the myelopathy. Because lymphocytapheresis is one of various immune therapies, we hope that more data concerning these therapies will be accumulated.

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